> Cancer or precancerous states as well as allopecia cannot be prevented with pharmaceutical drugs.

The Examiner cites the Wands factors but does not provide any analysis of these factors in the Official Action. The Examiner merely concludes that the claims are not enabled. This rejection is respectfully traversed.

Initially, Applicants respectfully rebut several of the statements made by the Examiner. The Examiner alleges that the diseases in Claim 15 are unrelated. As Applicants have pointed out in the previous response, the diseases of Claim 15 are associated with abnormalities of differentiation or proliferation and cited support in the specification for this proposition. Additionally, Applicants supplied the Examiner with a review article (*Current Pharmaceutical Design* 6:25-58 (2000)) that highlights the role of retinoic acid receptors in many of the disease states listed in Claim 15. Applicants also respectfully submit that the Examiner has not provided any support for the position that many of these diseases cannot be treated with a pharmaceutical drug. Applicants respectfully request that the Examiner cite scientific publications in support of this proposition as Applicants have come forward with published evidence to the contrary. Alternatively, if the Examiner's statement is based on personal knowledge, Applicants respectfully request that the Examiner provide Applicants with an Examiner's affidavit pursuant to 37 C.F.R. § 1.104(d)(2).

The Examiner has also asserted that cancer or precancerous states as well as allopecia cannot be prevented with pharmaceutical drugs. Again, Applicants request that the Examiner supply published evidence supporting this proposition or provide Applicant's

with an Examiner's affidavit if based on personal knowledge. Applicants particularly note that allopecia is recognized by one skilled in the art as capable of being prevented by hair loss inhibitors. Applicants also point the Examiner's attention to the *Current Pharm. Design* article previously submitted on June 26, 2002 with the Reply and Amendment. On page 45, the article states, "For example, retinoids block several actions of TPA, including tumor promotion, induction of the polyamine synthetic enzyme ornithine decarboxylase (ODC), and an initial phase of TPA-induced hyperproliferation in normal skin." TPA is a well-known tumor inducing agent. In a later section entitled "Cancer Therapy" of the same article on page 49, it is stated, "Retinoids are among the most widely studied cancer chemopreventative agents." In the same section, it is also observed, "Isotretinoin has been used successfully in the treatment of oral leukoplakia with concomitant restoration of normal RAR-β expression and also as a **chemopreventative** agent for second tumors in head and neck cancers." Thus, retinoic acid compounds are recognized in the art for their ability to prevent cancer and precancerous states.

Applicants turn now to the Wands factors cited, but not analyzed, by the Examiner. These factors include 1) breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988).

First, Claim 15 is not unduly broad. It merely encompasses numerous disease states recognized in the art to be associated with disordered differentiation and/or proliferation and modulated by retinoic acid receptor activation or inhibition. This is clearly demonstrated in the *Current Pharm. Design* review article. This article described retinoids as recognized modulators of, to name a few, skin proliferation and differentiation (cancer, keratinization disorders), psoriasis (skin disorder with immunological component), acne (disorder of sebaceous functioning), reversal of photoaging (combating aging, treatment of skin disorders due to U.V. radiation exposure), cancer, diabetes and metabolic diseases, and vascular effects. Thus, the present claim is not broader than an art recognized categorization of diseases.

Claim 15 relates to the treatment of diseases in an art-recognized category influenced by retinoic acid receptors. As discussed above, and as can be observed from the *Current Pharm. Design* article, the state of the prior art, the level of one of ordinary skill, and the level of predictability in the art are high.

Moreover, the specification provides working examples of synthesizing 70 compounds and various formulations of these. In addition, the specification indicates that methods of testing retinoic acid receptor modulators are well-known in the art and gives exemplary procedures. The Examiner still has not provided any technical reasoning as to why one skilled in the art cannot select a compound of the invention, determine its activity at a retinoic acid receptor using the methods disclosed in the specification and previously known in the art and proceed with using the compound to prevent or treat the disorders of Claim 15. Specifically, the Examiner has provided no evidence of what experimentation

one skilled in the art would engage in that would be considered undue based on the content of the disclosure and the knowledge in the art.

Finally, Applicants direct the Examiner's attention to, *e.g.*, Claim 18 of U.S. Patent No. 6,030,952. A copy of this patent is enclosed for the Examiner's convenience. This patent discloses compounds which are modulators of retinoic acid receptors, much like the presently claimed invention. Claim 18 reads:

> A method for the treatment of a condition selected from the group consisting of dermatological conditions affecting differentiation and proliferation related keratinization disorders; inflammatory and immunoallergic related keratinization disorders; cutaneous, mucous, ungual, and arthropathic psoriasis; cutaneous and respiratory atopy; gingival hypertrophy; inflammatory conditions without a keratinization disorder; viral, non viral, benign and malignant dermal and epidermal proliferations; ultra-violet radiation induced proliferations; bullosis and collagen diseases; ophthalmological disorders; aging of the skin; the stigmata of epidermal and dermal atrophy induced by local and systemic corticosteroids; cicatrization disorders and vibices; cicatrization, sebaceous function disorders; cancerous and precancerous states; inflammatory disorders; alopecia; immune related dermatological disorders; disorders of the cardiovascular system, non-insulin dependent diabetes related cutaneous disorders; which method comprises administering an effective amount of the compound of claim 1 to a patient in need of such treatment.

As the Examiner will undoubtedly note, this claim encompasses most, if not all, of the same diseases found in Claim 15 of the presently claimed invention. Clearly, the art recognizes the interplay of retinoic acid receptors and their modulators in many disease states. Certainly, the U.S.P.T.O. recognizes this as well in issuing this patent.

In light of the above remarks, Applicants respectfully submit that Claim 15 is enabled. Accordingly, withdrawal of this rejection is respectfully requested.

II. Rejection of Claims 1-13 and 15-20

Claims 1-13 and 15-20 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled. This rejection is respectfully traversed.

The initial burden of setting forth a reasonable explanation as to why the scope of protection provided by any claim is not adequately enabled by the description of the invention provided in the specification is on the Office. *In re Wright*, 999 F.2d 1557, 1562, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). The standard for determining whether the enablement requirement has been met is whether the experimentation needed to practice the invention is undue or unreasonable. M.P.E.P. § 2164.01 referring to *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916). To object to a specification on the grounds that the disclosure is not enabling with respect to the scope of a claim sought to be patented, the examiner must provide evidence or technical reasoning substantiating those doubts. *Id.* and M.P.E.P. § 2164.04. Additionally, without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *In re Wright*, 999 F.2d 1662, 27 U.S.P.Q.2d 1513; *In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971).

Bearing these standards in mind, Applicants turn to the Examiner's analysis of the Wands factors applied to the present case. In terms of breadth, the Examiner argues that R2 and R3 forming an 5-6 member adjacent aromatic ring is unduly broad. Claim 1 recites, "R_2 and R_3 taken together can form, with the adjacent aromatic ring, a 5- or 6-member saturated ring optionally substituted with methyl groups and/or optionally interrupted with an oxygen or sulphur atom." The Examiner argues that all 5-6 member

saturated rings are not enabled. Applicants respectfully submit that they have provided working examples which entitle Applicants to the full scope of this recitation. For example, *at least* Examples 2-6, 43, 44, 46, 47, 49, 50-59, 61, 62, 66, and 67 provide examples of saturated rings optionally substituted with methyl groups. Further, Example 10 contains a 6-member ring interrupted by sulfur.

The Examiner further rejects the recitation of R' and R'' forming a heterocycle ring with the nitrogen atom in Claim 1 as part of the R_1 moiety. The Examiner has not, however, provided any scientific or technical reasons as to why such a recitation is unduly broad. Further, the scope of the claims are to be analyzed as a whole. M.P.E.P. §2164.08. The Examiner merely selects several subparts of the claim and discusses why those particular subparts are allegedly not enabled, rather than evaluating the claim as a whole. Moreover, as discussed in detail below, Applicants respectfully submit that the 70 working examples of compound synthesis and 10 examples of formulations of the compounds adequately enable the full scope of the claims.

The Examiner also rejects the recitation in Claims 6 or 7 as not enabling for, *e.g.*, electron-withdrawing groups such as nitro existing in the ortho position on rings in these claims. Initially, Applicants point out that the claims 6 or 7 do not specifically recite the ortho position. The Examiner asserts that it is impossible for electron-withdrawing groups to exist in the ortho position on an aralkyl or aryl ring. Applicants respectfully submit that the Examiner has not provided any support for this bold assertion and request that evidence to this effect be provided. If such a statement is being made on personal knowledge, Applicants request that the Examiner provide an Examiner's affidavit to this effect.

Moreover, even assuming *arguendo* that the claim language encompasses some inoperative embodiments, this does not render the claim non-enabled. If one skilled in the art could determine which embodiments would be operative or inoperative with expenditure of no more effort than is normally required in the art, then the claim is considered enabled. *Atlas Powder Co. v. E.I.duPont Nemours & Co.*, 750 F.2d 1569, 1577, 224 U.S.P.Q. 409, 414 (Fed. Cir. 1984), *See also, In re Angstadt*, 537 F.2d 498, 502-03, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976) (undue experimentation not involved in determining operability v. inoperability). Thus, if it is apparent to (or could be readily determined via experiment by) one skilled in the art that a particular substituent would be unfavorable (or impossible, as the Examiner alleges), this is not sufficient to invalidate the claim as non-enabled.

The Examiner argues that the Markush groups encompassed by the three above-identified recitations are too broad because they encompass a much wider group of radicals than those actually tested. On the contrary, as is well understood, an applicant need not have actually reduced the invention to practice prior to filing the application. *Gould v. Quigg*, 822 F.2d 1074, 1078 and M.P.E.P. § 2164.02. The complete lack of a working example is a factor only to be considered in a case involving unpredictable and undeveloped art. M.P.E.P. § 2164.02. However, an applicant need not describe all actual embodiments. *Id.* Even assuming *arguendo* that one considers the chemical arts to be "unpredictable," the specification provides adequate guidance in the form of numerous working examples. Thus, the Examiner's statement does not support a finding of indefiniteness based on claim breadth.

The Examiner summarizes the nature of the invention as compounds useful as cosmetic compositions for body and hair hygiene. Applicants take exception to the narrow interpretation of the invention. As the specification (and the present claims, particularly Claim 15) clearly indicate, the compounds of the invention are useful for many purposes including, *inter alia*, pharmaceuticals for treatment of skin disorders, cancer, aging, corneopathies, and inflammatory disorders. Accordingly, the Examiner's characterization of the present invention is only partly correct.

In terms of the level of predictability in the art, the Examiner asserts that this is low and that Applicant "does not conduct any tests of these compounds for their effects as cosmetic compositions." Applicants respectfully submit that the level of predictability in this area is high. First, the Examiner does not address the level of predictability with regard to actually making these compounds. The Examiner has not provided any evidence as to why one skilled in the art, given the guidance in the specification and the level of skill in the art, would find the making of the compounds unpredictable. Second, the level of predictability of the use of these compounds is not low. Testing of retinoic acid compounds has been taking place for many years. In fact, the specification contains methods of determining whether a compound is a retinoic acid compound is an agonist or antagonist (see page 13, line 25 to page 15, line 7). Once this information has been obtained, one can predict the effect in a particular tissue based on the large body of knowledge that has accumulated in the field of retinoic acid receptor research (see *Current Pharm. Design* article containing over 216 references). Cosmetic testing is quite routine, thus, the Examiner argument that no cosmetic testing was presented in the specification is does not

support a finding of non-enablement. Applicants further note that the Examiner again presents only a conclusory statement rather than findings of fact. According to M.P.E.P. § 2164.04, an examiner should make specific findings of fact, supported by the evidence and then drawing conclusions based on the findings of fact. The mere allegation that the specification does not describe cosmetic testing is insufficient to support a conclusion that predictability is low.

The Examiner argues that the amount of direction provided by the specification is poor because only one type of heterocycle ring, nicotinate, is exemplified. The Examiner also argues that the guidance is poor because, *e.g.*, the synthesis of a compound with two nitro groups existing in the ortho position was not described. Initially, as noted above, Applicants point out that Examples 10, 11, and 12 contain an R_2-R_3 ring interrupted with a heteroatom, sulfur. Second, the Examiner has failed to indicate why one skilled in the art could not make other heterocycle rings based on the disclosure which demonstrates heterocycle rings with nitrogen atoms, which are exemplary heterocycles. Findings of fact as to why such extrapolation requires more than routine experimentation are necessary. Third, the fact that a the synthesis of a particular compound is not described is not dispositive. Applicants provide seventy (70) working examples of various compounds of the invention. Simply because a particular compound chosen at random by the Examiner in the genus claimed is not exemplified does not support a finding of non-enablement.

The Examiner asserts that there are no working examples of testing the compounds of the inventions as cosmetics. As noted above, the nature and utility of the presently claimed invention is much broader than just cosmetics. Moreover, working examples are

not required. At any rate, the testing of cosmetic compositions is routine, and as discussed above, so is the testing of compounds for retinoic acid receptor antagonism or agonism.

The Examiner finally asserts that undue experimentation would be required to practice the presently claimed invention based on the other above-mentioned Wands factors. However, as shown above, the Examiner's analysis is based on conclusory statements unsupported by specific findings of fact. Accordingly, the Examiner has failed to establish a *prima facie* case of non-enablement. Withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claim 10 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Examiner argues that the recitation of "amino acid residues are selected from a group consisting of residues derived from lysine, glycine, and aspartic acid" lacks antecedent basis. This rejection is respectfully traversed.

Claim 1, from which Claim 10 depends recites, "R' and R'', which may be identical or different, represent a hydrogen atom, a lower alkyl radical, an optionally substituted aryl radical or an amino acid residue..." (See page 4, lines 11-12 of Reply and Amendment filed June 26, 2002). Thus, Applicants respectfully submit that the amino acid residues in Claim 10 do have antecedent basis. However, Applicants are willing to entertain any suggestions by the Examiner that she believes would clarify the claimed invention. Accordingly, withdrawal of this rejection is respectfully requested.

Conclusions

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

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